Clin. exp. Immunol. (1991) **85**, 1–2 ADONIS 000991049100184H

EDITORIAL REVIEW

Antigen shedding and metastasis of tumour cells

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(Accepted for publication 19 April 1991)

Release of membrane surface antigens appears to be a common feature of malignant cells (Black, 1980; Baker *et al.*, 1982). The antigens have been detected in culture media of active growing cell lines *in vitro* (Komada *et al.*, 1987; Chiba *et al.*, 1989) and in the body fluids of humans and animals with various malignant tumours *in vivo* (Komada *et al.*, 1990; Vinuela *et al.*, 1991). The antigens detected were not confined to any particular molecule: they include the MHC antigens (Tsujisaki *et al.*, 1987), other differentiation antigens (Kay *et al.*, 1988; Komada *et al.*, 1990), tumour-specific/associated antigens (Fauget & Agee, 1989; Chiba *et al.*, 1989), and, in this issue of *Clinical and Experimental Immunology*, the intercellular adhesion molecule-1 (ICAM-1) (Tsujisaki *et al.*, 1991). In the case of cultured cells, the amount of antigen shed appears to correlate with cell growth and not cell division or cell death (Chiba *et al.*, 1989) whereas in patients, the level of antigens in bodily fluids seems to correlate with the clinical stage of the tumour (Fauget & Agee, 1989; Komada *et al.*, 1990).

When a cell is engaged in active growth, the general increase in cellular content, including molecules that constitute the membrane, may be taken as proportional to the increase in cell volume. The increase in membrane components is therefore in disproportionate excess compared with the increase in cell surface area, which varies, with approximation, as the 2/3rd power of the cell volume on the assumption that some simple balance of cell volume and cell surface area is to be maintained. The excess membrane must be disposed of, and one of the possible means is the shedding in the form of vesicles. Indeed, extensive shedding had been observed in different tumour cell lines by electron microscopy. Vesicles were either recovered in the pellets upon ultracentrifugation of tissue culture supernates and ascites fluid (Dvorak *et al.*, 1981), or observed as outgrowths from the parent cell body (Chiba *et al.*, 1989). In addition, the shedding of vesicles from the rat fibrosarcoma (Chiba *et al.*, 1989) was observed when cultured in 10% fetal calf serum (FCS) but not when under less encouraging growth conditions of 1% FCS. Other mechanisms of antigen release have also been suggested, including their proteolysis and the secretion of variant forms (Kay *et al.*, 1988).

ICAM-1 was first described by Rothlein *et al.* (1986) as an adhesion molecule that participates in leucocyte function-associated antigen-1 (LFA-1) dependent homotypic adherence of phorbol-ester-activated leucocytes and was subsequently established to be the counter-receptor for LFA-1 (Martin & Springer, 1987). The LFA-1/ICAM-1 interaction is important in a number of leukocyte adhesion activities (Makgoba *et al.*, 1988a) including the conjugate formation between cytolytic T cell and their targets (Makgoba *et al.*, 1988b) and natural killer (NK) mediated cytolysis (Kohl *et al.*, 1984; Timonen, Patarroyo & Gahmberg, 1988). It is generally recognized that NK cells are involved in the surveillance and regulation of tumour metastasis (Herberman & Ortaldo, 1981; Storkus & Dawson, 1991): the metastatic potential of tumour cells, in their blood-borne phase, shows a negative correlation with their sensitivity to NK cytolysis (Kawano *et al.*, 1986; Greenberg *et al.*, 1987) and the depletion of NK cells in mice results in enhanced susceptibility of the animals to malignancy (Hanna & Burton, 1981; Kawase *et al.*, 1982; Wiltrout *et al.*, 1985; Seaman *et al.*, 1987). Thus, the expression and shedding of ICAM-1 by tumour cells, as reported by Tsujisaki *et al.* (1991) in this issue, may have profound implications for the metastasis of tumour cells and for its regulation by cells of the immune system in terms of the tumour cells escaping surveillance by the shedding of certain membrane antigens.

The expression of ICAM-1 on tumour cells is stimulated by interferon-gamma (IFN-γ), and perhaps other cytokines, probably as a result of some form of tumour-induced T cell activation. The immediate consequence would be the enhancement of sensitivity of the tumour cells to LFA-1/ICAM-1-dependent adhesion and cytolysis. The increase of expression of ICAM-1 on fibroblasts surrounding the tumour nests may promote the adhesion NK cells to fibroblasts. Since this interaction is probably insufficient to induce NK cytolysis of fibroblasts, it is transient and may serve to direct the migration of NK cells towards the tumour target. If the tumour cells, or a sufficient number of them, survive this phase of surveillance, active growth may lead to the shedding of ICAM-1-containing membrane vesicles which, by interacting with LFA-1 on NK and other effector cells, would revert the balance to favour the survival and further growth, and eventually the metastasis, of the tumour cells. This view is consistent with the observation that IFN treatment of tumour cells can provide protection against NK cytolysis and enhance their metastatic capacity (Welsh *et al.*, 1981; McMillan *et al.*, 1987).

Other antigens and molecules in the vesicles shed from tumour cells may also play a role in their survival. Disproportionate shedding of tumour antigen may deplete the parent cell of tumour antigen (Chiba *et al.*, 1989), thus making them invisible

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to the host immune surveillance system. Alternatively, tumour-specific antigens on shed vesicles can absorb circulating antibodies thus neutralizing their anti-tumour effects (Vinuela *et al.*, 1991). Promotors of coagulation have been detected in shed vesicles; it is argued that they may induce clotting in the proximity of the tumour, thus forming a barricade to isolate the tumour from cells of the host immune system (Dvorak *et al.*, 1981).

The measurement of the level of shed antigens in body fluids may provide a convenient means to monitor the clinical state of cancer patients. Such a correlation had been documented for CD9 in the cerebrospinal fluid of patients with acute lymphoblastic leukaemia (Komada *et al.*, 1990), and for IL-2 receptors as well as tumour-associated antigens in the serum of patients with B-chronic lymphocytic leukaemia (Kay *et al.*, 1988; Fauget & Agee, 1989). It now appears that the presence of circulating ICAM-1 may provide a general indication of malignant disease incidents.

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